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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/729,156	12/05/2003	Shaomeng Wang	UM-08477	1029

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EXAMINER	
HUI, SAN MING R	

ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 12/01/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/729,156	WANG ET AL.	
	Examiner	Art Unit	
	San-ming Hui	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 September 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,27-41,43-47,49,50,52-55,60,61,78-80,82-93 and 96* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,27-41,43-47,49,50,52-55,60,61,78-80,82-93 and 96* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendments filed September 1, 2006 have been entered. Claims 3-26, 42, 48, 51, 56-59, 62-77, 81, and 94-95 have been cancelled. Claims 1, 2, 27-41, 43-47, 49-50, 52-55, 60-61, 78-80, 82-93 and 96 are pending.

The outstanding rejection under 35 USC 103(a) over Shelley, '367, and Merck Manual is withdrawn in view of the amendments filed September 1, 2006 since the instant claims are no longer encompass the use of hemigossypolone.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 27-41, 43-47, and 49-50 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for gossypol compounds that are having aldehyde groups and isopropyl group, does not reasonably provide enablement for apogossypol, the Schiff's base thereof that do not have aldehyde group on the gossypol compounds. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. In the instant case, the specification fails to provide sufficient information to one of skilled in the art to practice the instant invention.

The claims are directed to a method of treating proliferative disease, such as cancer. In the instant specification, only (-)-gossypol is demonstrated to have anti-tumor activity. Shelley, et al., Anticancer Drugs, 2000;11(3):209-216, clearly teaches that **apogossypol** is inactive against four tumor cell lines (See page 212, Figure 2). Shelley et al. further discusses that the reasons for apogossypol and the Schiff's base of gossypol to be inactive is due to the fact that the aldehyde groups are missing (See page 214, col. 2). Furthermore, the **ethyl derivatives of gossypol** show negligible inhibitory activity to the tumor cell lines similar to that of the Schiff's base derivatives (See page 214, col. 2, second paragraph). In other words, the evidence is clear that "when both of the aldehydes are blocked, forming the individual *l*- and *d*-bis Schiff's bases, the cytotoxicity activity is abolished." See page 214, last sentence bridging to page 215, first paragraph). Since the instant specification only demonstrates the activity of (-)-gossypol, there is no information as to how other derivatives, which without the aldehyde groups nor the isopropyl group, might be useful in a method of treating proliferative disorders. The instant specification fails to provide sufficient information to one skilled in the art to practice the full scope of the invention.

Response to arguments

Applicant's arguments filed September 1, 2006 averring apogossypol as enabled due to the reference by Becattini et al. have been considered, but are not found persuasive. Examiner notes that Becattini et al. is published in 2004, which is a post-filing date reference. Enablement has to be established at the time of filing (See MPEP

2164.05(a)). Therefore, Becattini et al. cannot be a probative evidence for enablement of the instant invention.

Applicant's arguments filed September 1, 2006 averring Shelley citing Liang not discussing ethylgossypol have been considered, but are not found persuasive. Shelly clearly discusses the anti-tumor activity of some gossypol derivatives, including ethyl, propyl, butylamine, and isopropyl derivatives of gossypol. It further states, "only the isopropyl derivative showed activity comparable to gossypol 1a in two of the three cell lines. The other three derivatives had negligible inhibitory activity at doses up to 25μM, which is similar to our present study using the L-phenylalanine methyl ester Schiff's base 1c of gossypol." See page 214, col. 2, second paragraph, the last couple sentences). Therefore, it is clear that the anti-tumor activity the ethyl derivative of gossylpol possessed is negligible, regardless whether it is similar to that of the Schiff's base of gossylpol.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 52-55, 60-61, 78-80, 82-93, and 96 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 6,114,397 ('397) from IDS filed October 17, 2005 in view of Merck Manual of Diagnosis and Therapy, 16th ed., 1992, pages 1275-1277.

'397 teaches a method and composition of employing gossypol, gossypol acetic acid, gossypolone and metabolites as effective in treating cancer (See for example the abstract and claims 1-14). '397 also teaches gossypol can be combined with other anti-cancer therapeutic agents such as cisplatin in a method and composition of treating cancer (see abstract and col. 2, line 65 - col. 3, line 11).

'397 does not expressly teach the use of radiation in combination with gossypol compounds to treat cancer. '397 does not expressly teach the herein recited regimen of the compounds used such as route of administrations and the sequence of

administration. '397 does not expressly teach the method of treating cancer employs the optical isomers gossypol compounds.

Merck Manual teaches that radiation is one of the common modalities in cancer treatment (See page 1276-1277).

It would have been obvious to one of ordinary skill in the art at the time of invention to employ both radiation and gossypol compounds of '397, as racemic or pure enantiomers, in a method and composition of treating cancer. It would have been obvious to one of ordinary skill in the art at the time of invention to optimize the therapeutic regimen of the cancer treatment employing the gossypol compounds and radiation.

One of ordinary skill in the art would have been motivated to employ both radiation and gossypol compounds of '397, as racemic or pure enantiomers, in a method and composition of treating cancer. Since both radiation and gossypol compounds of '397 are known to be useful in treating cancer individually, combining them in a composition or concomitantly employing them in a method of treating the very same disease (i.e., cancer) would be prima facie obvious, at least additive effect would be expected. '397 teaches a chiral center in the claimed compound, and illustrated separation for such optical isomers. It is well settled patent law that the skilled artisan, knowing a compound contains an asymmetric carbon atom, possesses all resultant optical isomers. The skilled artisan in possession of the designated compounds, possesses all isomeric forms of the compound for the old and well known antitumor utility. It is well known in the pharmaceutical art that various optical isomers will exhibit

biological effects at various levels. Absent some difference in kind between the various isomers the skilled artisan would have seen each isomer as *prima facie* obvious (see *In re Adamson and Duffin*, 125 USPQ 233 (CCPA 1960)). The skilled artisan would have expected optical isomers to be separable and isomers so separated to exhibit physiological effects at varying levels. Possessing a compound known to contain chiral centers, places all the resultant compounds in the skilled artisan's possession. It would follow therefore, the instant claims recite *prima facie* obvious subject matter and are properly rejected under 35 USC 103.

One of ordinary skill in the art would have been motivated to optimize the therapeutic regimen of the cancer treatment employing the gossypol compounds and radiation since optimization of the resulted parameters (e.g., dosage and regimen) is routinely done in the art and thus obvious as being within the purview of skilled artisan.

Examiner notes that the herein claimed mechanism of action of gossypol must be present in the method suggested by the cited prior arts since the products and its intrinsic properties cannot be separated.

Response to arguments

Applicant's arguments filed September 1, 2006 averring the presence of the synergistic effects have been considered, but are not found persuasive. It is applicant's burden to demonstrate unexpected results over the prior art. See MPEP 716.02, also 716.02 (a) - (g). Furthermore, the unexpected results should be demonstrated with evidence that the differences in results are in fact unexpected and unobvious and of

both statistical and practical significance. *Ex parte Gelles*, 22 USPQ2d 1318, 1319 (Bd. Pat. App. & Inter. 1992). Moreover, evidence as to any unexpected benefits must be "clear and convincing" *In re Lohr*, 137 USPQ 548 (CCPA 1963), and be of a scope reasonably commensurate with the scope of the subject matter claimed, *In re Linder*, 173 USPQ 356 (CCPA 1972). In the instant case, the alleged synergistic effect are not seen in all cases, for example in Fig.16, the Breast cancer cell survival rate for (-)-gossypol is similar to that of Taxol + (-)-goosypol when the concentration of (-)-gossypol as above 10μM. Furthermore, the scope of the claim is much broader than that of the showing. For example, the examples in the specification are limited to only (-)-gossypol and not other gossypol derivatives. The cancer cell showing are also limited. The secondary agents are essentially limited to taxol. However, the scope of the instant claims encompassed far more than what were shown in the specification. Therefore, the cited prior arts still render the instant claims obvious.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to San-ming Hui whose telephone number is (571) 272-0626. The examiner can normally be reached on Mon 9:00 to 1:00, Tu - Fri from 9:00 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan, PhD., can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

San-ming Hui
Primary Examiner
Art Unit 1617